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VALUE IN HEALTH

The Effect of Disease, Functional Status, and Relapses on the Utility of People with Multiple Sclerosis in the UK

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ABSTRACT

Objectives: Because published utility estimates in multiple sclerosis (MS) are concentrated in people with moderate to severe disease severity and focus on specific types of MS, we conducted a cross-sectional study of people with MS to estimate the utility associated with disease, functional status as measured by the Adapted Patient Determined Disease Steps (APDDS) Scale, and relapse to enhance knowledge of the association of these factors and utility.

Methods: The study was conducted by a postal questionnaire sent to 12,968 people in a database managed by a UK charity (the MS Trust). Utility was assessed using the EQ-5D multiattribute utility scale. The APDDS is closely related to the more commonly reported Expanded Disability Status Scale (EDSS).

Results: A total of 2708 (20.9%) questionnaires were returned and 2048 (15.8%) respondents provided data suitable for analysis. The mean age of the sample was 51 years, and 22.5% of people were aged 60 years or more. Disease severity was concentrated in people with moderately severe MS (EDSS 4–6.5), with 21%, 60%, and 19% of people reporting mild, moderate, and severe disease, respectively. Results show that disease severity has an inverse relationship with utility. The mean utility is 0.491. Utility varies between 0.870 and –0.195 for EDSS states 0 and 9. Number of years since diagnosis, type of disease, and recent relapse status are also all significantly associated with utility.

Conclusions: The results are comparable with previous published utility estimates. We have demonstrated a clear relationship between functional status, disease type, relapse status, duration of illness, and utility. As a set of coefficients, the utility estimates we have calculated may be used to compare the quality of life of people with MS with other illnesses and to inform future economic evaluations in MS.

Keywords: EQ-5D, multiple sclerosis, study, utility.

Introduction

Multiple sclerosis (MS) is a neurological disease characterized by areas of demyelination (lesions) within the central nervous system. These lesions affect the normal functioning of the nerves involved and an accumulation of MS lesions over time result in irreversible physical and neurological impairment [1]. People with MS can experience acute exacerbations of symptoms with periods of stable disease in between (relapsing-remitting MS or RRMS) or there can be a gradual increase in disability over time with or without acute relapses (primary progressive MS or PPMS). People with the remitting form of MS can subsequently experience progressive disease (secondary progressive MS or SPMS).

The prevalence of MS across England and Wales is approximately 110 per 100,000 people (thought to vary by latitude from 104 per 100,000 on the south coast of England to 155 per 100,000 in the Scottish borders) [2]. It is common in young and middle-aged adults and thus can strike during a person's most economically productive and active years and during the period when major life decisions are made.

Two disease severity scales are used in the study and frequently referred to: The clinician rated Expanded Disability Status Scale (EDSS) [3]; and the self-rated Adapted Patient Determined Disease Steps (APDDS) scale, which is a refinement of the Patient Determined Disease Steps (PDDS) scale [4; G. Kobelt, Pers. Comm., 2005]. The degree of physical disability and neurologic impairment in MS is usually measured quantitatively using the Kurtzke Functional System scores (FS) and EDSS. The EDSS is based on a standard neurological examination. Seven functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, and mental functions) are rated. These ratings are then used in conjunction with observations and information concerning gait and use of assistive devices for ambulation to reach an EDSS score. The FS is an ordinal (or nonlinear) clinical rat-

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ing scale ranging from 0 to 5 or 6. The EDSS is also an ordinal clinical rating scale ranging from 0 (normal neurologic examination) to 10 (death due to MS) in half-point increments. The EDSS is recognized as the gold standard and is used frequently as an outcome measure in clinical trials [5]. The APDDS is a refinement of the PDDS [4]. The objective for the development of the PDDS was to produce a simple and reproducible assessment of functional disability in MS for self-assessment by people with MS that mapped to the EDSS scale. The PDDS is based on the earlier Disease Steps scale developed by Hohol et al. [6] Hohol assessed the Spearman rank correlation coefficient between Disease Steps and EDSS in 1323 people with MS and found it to be very strong (0.958), which supports comparison with EDSS. The APDDS was found to be equivalent to EDSS, except that APDDS 7, 8, 9, and 10 equated to EDSS 6.5, 7–7.5, 8–8.5, and 9–9.5, respectively.

It is clear that MS has a detrimental impact on health-related quality of life (HRQoL) and utility. Gruenewald et al. undertook a systematic review of HRQoL and multiattribute utility scales (MAUS) used in MS and provided a summary of the literature [7]. MAUSs are measures of health status. They are standardized multidimensional health state classifications with pre-existing preference or utility weights, which generate a single index score for each state of health where full health is one and zero is equivalent to death [8]. MAUSs can have scores of less than zero for health states regarded as worse than death. MAUSs have become an important set of instruments for estimating the health state values used to calculate quality-adjusted life-years (QALYs) and are widely used in economic evaluations to value the benefits of health care. Previous studies have reported MAUS utility estimates for persons with MS in the UK [8,9]; however, there is a paucity of data in mild disease (EDSS 0–3.5) and each focuses on a specific type of MS [9,10].

Despite the debilitating nature of MS, there are treatments available, albeit ones of modest efficacy. The Association of British Neurologists (ABN) guidelines recommend that two types of treatment (beta interferon and glatiramer acetate) should be made available to a well-defined subgroup of people with MS [11]. The ABN guidelines advocate treatment to reduce relapses and delay disease progression to a stage when the treated person is no longer able to walk.

A cross-sectional study was performed in a large representative sample of the UK MS population. In this article, we present the results of the analysis of utility data collected using a MAUS. The MAUS used is the EuroQoL 5-Domain self-report questionnaire (EuroQoL), incorporating the EQ-5D descriptive system [12]. The objectives of the analysis are to estimate the disutility of disease progression for people with MS and to quantify the disutility associated with an acute relapse. It is important for health policymakers to understand how the utility profile of a disease varies with disease severity so resources can be targeted appropriately.

Methods

Study Design

A cross-sectional study of people with MS in the UK was undertaken via a postal survey. The UK-specific questionnaire used in the survey was based on an established tool developed by Kobelt et al., which has formed the basis of previous cost-of-illness studies and includes a comprehensive range of resource use to estimate both direct and indirect costs [4,13]. A version of this questionnaire was verified against the medical records of a subset of respondents (n = 202) in the earlier study [13]. The questionnaire was amended and adapted to the UK setting after consultation with MS nurses, neurologists and experts at the MS Trust and MS Society. The questionnaire was checked to ensure it met the reporting requirements of the Medicines and Healthcare products Regulatory Agency (MHRA, Pers. Comm., 2005).

Distribution of Questionnaire

Questionnaires were distributed by the MS Trust (UK) to its database to ensure names and addresses remained anonymous. No personal data that would allow the respondent to be identified were collected on the questionnaire. The questionnaire was sent as an insert to the February 2005 edition of the UK MS Trust quarterly newsletter "Open Door" (circulation of 12,968). A covering letter explained the details of the study, and the circumstances in which the data were to be used. The respondent was required to sign a consent statement to indicate they had read and agreed with the terms of the study. It is recognized that some people with MS would be unable to complete a questionnaire themselves. Therefore, the instructions indicated that a carer could complete the questionnaire on behalf of the person with MS provided they had authority to do so, in which case the carer was required to sign the consent statement to indicate this. The completed questionnaire was returned to the investigators using a pre-addressed envelope. The number of questionnaires returned was 2708 (20.9%) and 2048 (15.8%) were suitable for analysis.

Outcomes Collected

Seven predictive variables were collected to evaluate the dependent variable, EQ-5D utility. The variables are shown in Table 1. Disease severity was measured using APDDS and reported by EDSS strata to aid comparison with other studies. Four predictive variables are used to assess the type of disease. Type of MS

Table 1 Variables assessed in the utility analysis

Element	Type	Variable
Demographics	P	Sex (male, female) Years since diagnosis Education (secondary school, college/sixth form, university/polytechnic, post graduate degree)
Disease severity	P	Adapted Patient Determined Disease Steps (APDDS) (0–10 scale)*
Type of Disease	P	Type of MS (PPMS, RRMS, or SPMS) Recent relapse during prior 3 months (yes or no) Estimated years since diagnosis as a proxy for disease duration (integer)
Treatment	P	Currently taking MS treatment (yes or no) Treatments: glatiramer acetate, interferon β-1a, interferon β-1b
Utility	D	EQ-5D (derived from EQ-5D descriptive system)

*Reported as EDSS to aid comparison with other studies.
Reference case: No recent relapse, EDSS 0, RRMS, Sex (female), Education (secondary school).
D, dependent variable; MS, multiple sclerosis; P, predictive variable; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.

(PPMS, RRMS, or SPMS) and recent relapse within the last 3 months are based on a categorical response to a description within the questionnaire. The disease and symptom modifying treatments for which data were collected are shown in Table 1. Respondents were provided with the generic and trade name of the treatments in the questionnaire.

Utility data were collected using EuroQoL. Utilities were assigned using the EQ-5D UK value set, which was obtained from a representative sample of the UK population using the time–trade-off method [14].

Data Management

Upon receipt, the questionnaire identifier was logged in an Access database (Microsoft Inc.) and the questionnaire checked to ensure the consent statement had been signed. Unsigned questionnaires and questionnaires received after the closing date were not included in the study.

The questionnaire was processed using specialized Optical Character Recognition (OCR) and form reading software called FormReader 6.0 (ABBYY Software House, Moscow, Russia). A sample of original questionnaire pages was compared with the OCR output and adjustments made to eliminate character recognition errors.

Incoming questionnaires were scanned and batch processed by the OCR and form reading software. An investigator reviewed any data point that failed the validation rules established in the OCR and form reading software.

Inter and intrafield validation was again performed within the Access database using queries to flag illogical or ambiguous data entries. These were checked against the original questionnaire to rule out data entry error and records containing invalid data were marked as censored and excluded from the analysis.

Analysis

Data were analyzed using Stats Direct 1.9.8 (StatsDirect Ltd, Attrinchaw U.K.). A multivariate linear regression analysis was undertaken to identify the predictive variables associated with the independent variable, EQ-5D utility. Data are expressed as mean and 95% confidence intervals. Analysis of variance (ANOVA) was undertaken from the regression and the multiple correlation coefficient (R^2) calculated. Differences were considered statistically significant at a value of $P < 0.05$.

Results

The distribution of questionnaires sent to people in England, Scotland, and Wales was approximately 87%, 8%, and 5%, respectively. It is not known whether the responses followed a similar distribution.

Table 2 shows the results of the censoring on the study population used in the analysis. Approximately

Table 2 Results of censoring on study population

Description	Questionnaires n (%)
Questionnaires mailed	12,968 (100.00)
Responses received	2,708 (20.89)
Unsigned or received after deadline	200 (1.54)
Type of MS: multiple selection no selection or "not known"	315 (2.43)
Type of MS: "SPMS" and APDDS < 2	3 (0.02)
Disease severity (APDDS): multiple selection or no selection	12 (0.09)
Utility (EQ-5D): multiple selection or no selection	130 (1.00)
Population for analysis	2,048 (15.79)

Table presented in the order the censoring was carried out. Individual responses could have been censored for more than one reason.
APDDS, Adapted Patient Determined Disease Steps; MS, multiple sclerosis; SPMS, secondary progressive MS.

Table 3 Demographic and disease information (n = 2048)

	Proportion (%)
Demographics	
Sex	
Male	24.7
Female	74.5
Missing	0.8
Age (mean 51.4) (years)	
18–29	1.4
30–39	13.8
40–49	27.0
50–59	35.3
60–69	18.0
70–79	4.2
80 or above	0.3
Education	
Secondary school	32.2
College or sixth form	26.5
University or polytechnic degree	29.7
Postgraduate degree	10.1
No answer	1.6
Disease information	
Mean age at first diagnosis:	38.8 years
Type of MS	
RRMS	35.5
SPMS	37.2
PPMS	27.3
EDSS level (disease severity)	
EDSS 0–3	21.3
EDSS 4–6.5	59.6
EDSS 7–9.5	19.1
Relapses during last 3 months	
Yes	28.9
No	71.1

EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.

76% (n = 2048) of respondents with a full data set are suitable for analysis. Censored responses are predominantly due to a lack of clarity regarding the type of MS, unsigned or late responses, and incomplete or missing data on utility (11.6% (n = 315), 7.4% (n = 200), and 4.8% (n = 130), respectively).

Table 3 presents demographic and disease information on the 2048 respondents in the analysis sample. Three quarters of respondents are female and the mean age of the sample is 51.4 years. The sample is well educated; approximately 40% of respondents have one or more degrees. First symptoms are reported at 32 years. The type of MS reported is slightly biased toward SPMS and RRMS disease, although all three types are well represented. More than three quarters of the population report moderate or severe disease (EDSS 4 or greater) and 29% of the sample reported a relapse in the preceding 3 months.

The distribution of the population by EDSS state follows a bimodal distribution (Fig. 1) with peak frequencies at EDSS 2 and EDSS 6. Few responses are available for EDSS states 0, 3, and 9.

The signatories to the survey are predominantly people with MS. The distribution of signatories between people with MS, carers or where it is not reported is approximately 92.5%, 6.4%, and 1.1%, respectively. A greater proportion of carers are signatories in higher EDSS states, with 44.2% and 75.0% in EDSS 8 and EDSS 9, respectively. The mean utility for EDSS 8 reported by carers is significantly lower than that reported by people with MS ($P < 0.0001$). There is no significant difference between signatories in EDSS 9.

The mean (standard deviation) utility for the study population is 0.491 (0.320).

There is a significant inverse relationship between EDSS and utility (see Fig. 2 and Table 4). Number of years since diagnosis as a proxy for disease duration, type of disease (SPMS), recent relapse status, and educational status are also all significantly correlated with utility. The PPMS coefficient approaches significance ($P = 0.063$).

A significant association was not found for all coefficients. In addition to PPMS, sex, and EDSS 1 are not significantly different from the reference case.

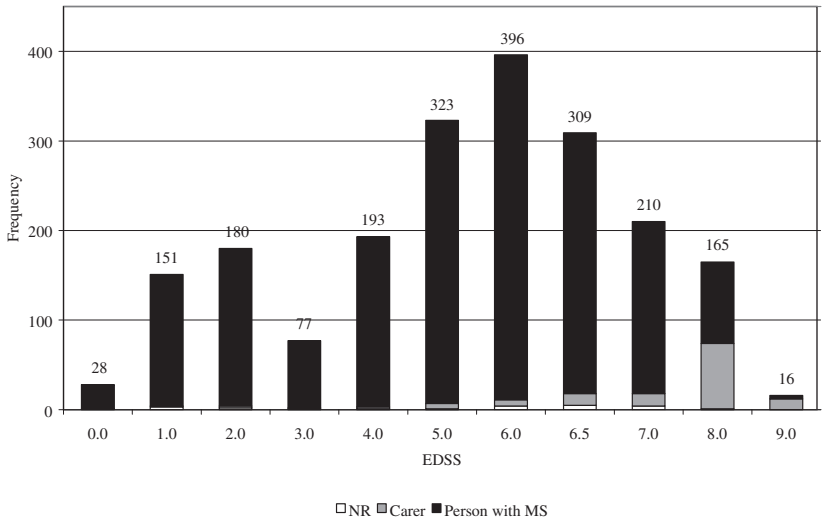

Figure 1 Distribution of Expanded Disability Status Scale (EDSS) states in the study according to signatory status. NR, not reported. Half points on EDSS not shown on graph axis except at EDSS 6.5.

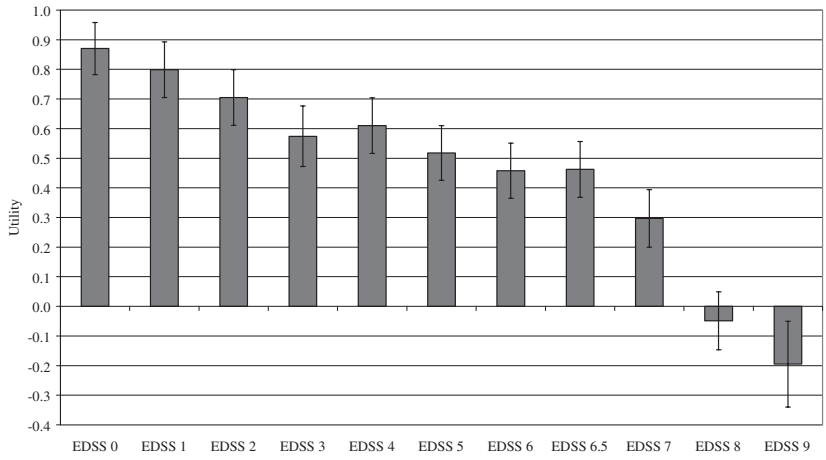

Figure 2 Relationship between Expanded Disability Status Scale (EDSS) and utility derived from EQ-5D using the EuroQoL instrument. Error bars depict 95% confidence intervals. Half points on EDSS not shown on graph axis except at EDSS 6.5.

The predictive power of the regression is high ($R^2 = 0.478$).

Discussion

This study confirms the impact that MS has on the utility of people with MS. It highlights the decrease in utility associated with an increase in disease severity as measured by the APDDS. The societal preference from the UK EQ-5D value sets assesses the utility of people living with the most severe stages of MS (equivalent to EDSS 8 and above) as worse than death.

We have also demonstrated that the type of disease (SPMS), a recent relapse, and length of time since diagnosis have an effect on the quality of life of people with MS. People with SPMS have a lower utility than people with RRMS (–0.045). PPMS also has a detrimental effect on utility compared with RRMS (–0.033) although the finding does not quite reach significance ($P = 0.063$). People with MS who have suffered a recent relapse also have a significant utility decrement (–0.071). The number of years since diagnosis has a positive effect on utility, with an approximate utility gain of 0.01 for every 5-year period with MS. The small positive correlation could be due to coping strategies adopted by people who have lived with the disease for a long time.

Table 4 Coefficients from regression analysis for utility derived from EQ-5D

Parameter	Coefficient	95% CI (lower, upper)	*P*-value
Reference case	0.870	(0.782, 0.958)	*
EDSS 1–1.5	–0.071	(–0.165, 0.023)	0.138
EDSS 2–2.5	–0.165	(–0.259, –0.072)	*
EDSS 3–3.5	–0.296	(–0.398, –0.195)	*
EDSS 4–4.5	–0.260	(–0.354, –0.167)	*
EDSS 5–5.5	–0.352	(–0.444, –0.260)	*
EDSS 6	–0.412	(–0.505, –0.319)	*
EDSS 6.5	–0.408	(–0.502, –0.314)	*
EDSS 7–7.5	–0.573	(–0.670, –0.477)	*
EDSS 8–8.5	–0.919	(–1.017, –0.820)	*
EDSS 9–9.5	–1.065	(–1.210, –0.919)	*
Recent relapse	–0.071	(–0.096, –0.046)	*
SPMS	–0.045	(–0.076, –0.014)	0.005
PPMS	–0.033	(–0.067, 0.002)	0.063
Education: College	0.029	(0.002, 0.055)	0.033
Education: University	0.057	(0.031, 0.082)	*
Education: Postgraduate	0.058	(0.022, 0.095)	0.002
Sex: Male	0.017	(–0.007, 0.041)	0.165
Years since diagnosis	0.002	(0.001, 0.003)	*
MS treatment	—	—	—

*$P < 0.001$.
Education: College, college or sixth form; University, university or polytechnic.
—, no association found; CI, confidence interval; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; PPMS, primary progressive MS; SPMS, secondary progressive MS.

The ABN recommends treating people with RRMS, and people with SPMS who are still experiencing frequent relapses, while the person is still able to walk (EDSS state ≤6.5). Their recommendations are based on the evidence of treatment effect that is concentrated in people who entered trials with an EDSS ≤5.5. Our study demonstrates that large utility losses could be avoided through delaying progression to EDSS states 7 and beyond. Research into the effects of disease modifying treatments on delayed disease progression from moderate to severe disease would help us understand the utility losses that could be avoided in this group of people [14].

Utilities of people with RRMS and SPMS have previously been reported [9,10]. The utilities reported by Parkin et al. and Forbes et al. compare closely with the utilities we derived except for those in EDSS 3 (0.71 Parkin et al. compared with 0.57 in the current study) and EDSS 5 (0.64 Forbes et al. compared with 0.52 in the current study). The utilities from the Parkin et al. study included some relapsing patients, however, and the study by Forbes et al. reported utility values compared with ambulatory categories that we subsequently mapped to EDSS state, so it is not possible to draw a direct comparison with our results.

The average utility of people with MS as measured in this study appears to be worse than all but one of the most prevalent conditions assessed by Currie et al.

Table 5 A comparison of the utility of people with MS and other prevalent conditions

ICD10	Disease	Mean	SD	N	Setting
M06	Other rheumatoid arthritis	0.432	0.310	120	OP
–	Multiple sclerosis (PPMS, RRMS, and SPMS)	0.491	0.320	2408	—
I25	Chronic ischemic heart disease	0.558	0.317	146	OP
R10	Abdominal and pelvic pain	0.576	0.350	74	OP
I20	Angina pectoris	0.576	0.306	284	IP
R07	Pain in throat and chest	0.589	0.346	472	IP
I21	Acute myocardial infarction	0.610	0.336	251	IP
I48	Atrial fibrillation and flutter	0.614	0.316	189	IP
I25	Chronic ischemic heart disease	0.636	0.293	789	IP
R10	Abdominal and pelvic pain	0.670	0.325	337	IP
K21	Gastroesophageal reflux disease	0.671	0.301	216	IP
H26	Other cataract	0.672	0.286	748	IP
E11	Noninsulin-dependent diabetes mellitus	0.674	0.287	159	OP
K50	Crohn's disease [regional enteritis]	0.692	0.293	73	OP
I10	Essential (primary) hypertension	0.694	0.306	82	OP
N95	Menopausal and other perimenopausal disorders	0.703	0.317	103	OP
K80	Cholelithiasis	0.709	0.305	192	IP
C61	Malignant neoplasm of prostate	0.718	0.278	83	OP
C44	Other malignant neoplasms of skin	0.726	0.267	273	IP
K51	Ulcerative colitis	0.787	0.235	61	OP
N92	Excessive, frequent, and irregular menstruation	0.804	0.250	116	OP

All conditions other than MS adapted from Currie et al. (2005) (tables 5 and 6) [15].
IP, inpatient; MS, multiple sclerosis; OP, outpatient; PPMS, primary progressive MS; RRMS, relapsing-remitting MS; SPMS, secondary progressive MS.

in a hospital setting (people with "other rheumatoid arthritis" attending a hospital outpatient department) [15]. Currie et al. evaluated the utilities of 10 most prevalent conditions in inpatients and outpatients attending a UK NHS Trust hospital using EQ-5D and the results have been adapted in Table 5. The observation is interesting because the MAUS (EQ-5D), country, and value sets used in both studies are the same; however, direct comparison should be treated with caution as the data collection method for each study differ. If Currie et al. subsequently publish utility estimates for people with MS it will be interesting to note how the values compare with this study.

The prevalence of the study population by EDSS state follows a bimodal distribution that has previously been cited by Richards in a review of several cross sectional studies [2]. The results are therefore generalizable to other populations.

There are a number of caveats with the analysis we performed.

Two reviews have examined the evaluation of quality of life in MS and reported that EQ-5D has low coverage of quality of life domains relevant to people with MS [7,16]. Mitchell et al. reported that EQ-5D covered three out of 11 domains; Gruenewald et al. reported coverage of 3 out of 15 domains relevant to people severely affected by MS (EDSS ≥6). It is likely that an alternative instrument to EQ-5D, which covered more domains of relevance to people with MS, would have resulted in different utilities.

We do not know what effect the alteration of a single word in the APDDS has on the correlation between APDDS and EDSS. The term "stick" replaced "cane" in APDDS states 4–6. The change was made after consultation with experts and we do not anticipate that it will have a significant impact on the results.

EuroQoL is a self-completed questionnaire, although we allowed carers to complete it where the person with MS was unable. Bias appears to have been introduced in EDSS 8–8.5, where carers report a significantly worse utility than people with MS. In another study of people with MS living in a community setting there was similar discordance noted between carers and people with MS in reported problems, where people with MS-reported depression, mood, and psychosocial issues less frequently than carers as the disease progressed [17].

As with any postal questionnaire study, respondents were self-selected and a "volunteer effect" has been previously reported [18]. Volunteers tend to be more intelligent, open to innovation, and extroverted than a random sample, although the effect of self-selection on the results is not known.

The bimodal distribution may be due to the similarity in the wording of APDDS 3 and APDDS 2, which could cause some respondents to ignore APDDS 3 and choose either APDDS 2 or 4, which are distinctly different. The APDDS 2 description is, "I have some noticeable symptoms from my MS (e.g., some muscle weakness, slight difficulties in walking, slight visual disturbances) but they are minor and have only a small effect on my lifestyle." The APDDS 3 description is similar, "I have symptoms as described above, but I don't have any limitations in my walking ability. However, I do have significant problems due to MS that limit daily activities in other ways."

The diagnosis of the type of MS and recent relapse status was made by the respondent and was not based

on a definitive clinical diagnosis and this could result in some miscategorization.

The coefficient calculated for recent relapse should not be used to infer a total utility loss associated with relapse. A longitudinal study would be required to determine this total utility loss.

Conclusion

Our results show that people with MS have a quality of life that deteriorates as the disease progresses until severe disability occurs in what some have described as a state worse than death at EDSS 8. SPMS and recent relapse are both indicators of further utility loss. People with MS that responded to the survey appear to live in a utility state that is equivalent or somewhat worse than all but one of the most prevalent conditions admitted to a UK inpatient or outpatient setting.

Research into existing and future MS treatments should measure the effect of treatment on the utility of people with MS to better help patients, clinicians, and health-care decision-makers evaluate the interventions. The designers of studies should consider evaluating treatments in greater numbers of people with moderate states of disability and impairment (i.e., EDSS 4, 5, and 6), because if the disease could be delayed in these people large then losses in utility could be avoided in EDSS ≥ 6.5.

Finally, the utility results have filled a gap in our knowledge and could be used in future economic evaluations in MS.

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